REMARKS

Applicants thank the Examiner for the telephonic conversation on June 26, 2003, concerning the sequence listing.

With entry of the current amendment, the inadvertent errors in the previous Sequence Listing have been corrected. The paper copy of the Substitute Sequence Listing provided herewith was printed from the floppy disk. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

This amendment adds no new matter.

The Substitute Sequence Listing submitted on April 4, 2003 corrected inadvertent errors in SEQ ID NOs:1 and 2. The present amendment also corrects errors in SEQ ID NOs:3 and 4 and SEQ ID NOs:7 and 8. In SEQ ID NO:3, at position 182, the nucleotide residue "C" was inadvertently replaced by an incorrect residue "T". This produced the codon "TTT", translated as "Phe" at position 61 in the amino acid sequence of SEQ ID NO:4. Similarly, in SEQ ID NO:7, at position 185, the nucleotide residue "C" was inadvertently replaced by an incorrect residue "T". This produced the codon "TTT", translated as "Phe" at position 62 in the amino acid sequence of SEQ ID NO:8. The current sequence listing corrects these errors. Support for the corrections is found, *e.g.*, on page 3 of the informal Sequence Listing labeled "SEQ ID NO:1/2" in the PCT application PCT/US99/06641, published as WO 99/50398. The first codon of the fourth line of nucleotides shows "tct" and the amino acid translation "ser" below. The corresponding correct positions in sequences on page 4, "SEQ ID NO:3/4," and on page 6, "SEQ ID NO:7/8," show the second codon of the fourth line of nucleotides to be "tct" and the amino acid translation "ser" below.

In addition, the present amendment corrects errors in SEQ ID NOS:16 and 17 and SEQ ID NOS:18 and 19. In SEQ ID NO:16, at position 113, the nucleotide residue "A" was inadvertently replaced by an incorrect residue "C". This produced the codon "ACC", translated as "Thr" at position 38 in the amino acid sequence of SEQ ID NO:17. Similarly, in SEQ ID NO:18, at position 39, the nucleotide residue "C" was inadvertently replaced by an incorrect

residue "A". This produced the codon "AAA", translated as "Lys" at position 13 in the amino acid sequence of SEQ ID NO:19. The current sequence listing corrects these errors. Support for the corrections is found, *e.g.*, on pages 11 and 12 of the informal Sequence Listing labeled "SEQ ID NO:16/17" and "SEQ ID NO:18/19" in the PCT application PCT/US99/06641, published as WO 99/50398. On page 11, the 18th codon of the second line of nucleotides is shown as "AAC" and the amino acid translation "asn" below, whereas on page 11, the 13th codon of the first line of nucleotides is shown as "AAC" and the amino acid translation "asn" below.

Restriction Requirement

Applicants thank the Examiner for rejoining claims 1-16 for examination. Claims 20-27 and 31-33 remain withdrawn from consideration. Claims 17-19, 28-30, 40, 43, and 44 were previously cancelled without prejudice. Accordingly, claims 1-16, 34-39, 41, and 42 are under examination.

Rejection under 35 U.S.C. § 112, first paragraph-enablement

Claims 1-16 were rejected as allegedly not enabled. The rejection alleges that the specification does not teach ribonucleases with at least 60% identity to SEQ ID NO:2 and that therefore the specification does not enable the claims. The Examiner had indicated that the main problem was the inaccuracies in the SEQ ID NOs (*see,* the Conclusion on page 6 of the July 3, 2003 Office Action). Applicants believe that these inadvertent errors have been corrected in the substitute sequence listing. To the extent that the rejection applies to the claims in view of the submission of the corrected sequence listing, Applicants respectfully traverse.

As the Examiner knows, it is well settled in the biotechnology art that routine screening of even large numbers of samples is not undue experimentation when a probability of success exists. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As stated in Wands, "enablement is not precluded by the necessity for some experimentation, such as routine screening." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, as set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments." The application provides guidance to make the claimed sequences

based on structural properties and guidance for performing assays to assess the function of the sequences. Thus, although such analyses could conceivably require analyzing a large number of sequences, the practitioner could reasonably expect to be able to successfully identify sequences that fall within the scope of the invention.

In the present case, claims 1-16 are drawn to recombinant ribonucleases (and cytotoxic reagents comprising the ribonucleases) that have a function, RNase activity, and structural features set forth in the claims, *i.e.*, the claimed proteins have particular residues at defined positions and at least 60% sequence identity to a reference SEQ ID NO. The application clearly teaches how to make and used the claimed ribonucleases. For example, the specification teaches how to determine percent identity using techniques and algorithms well known in the art (*see, e.g.*, page 9, line 11 through page 10, lines 31) and provides additional direction to identify and/or design RNases of the invention (*see, e.g.*, page 14, lines 21-32; page 15, line 22 through page 16, line 2; page 16, lines 8-16 and lines 19-23; page 16, line 26 through page 17, line 30; and page 18, lines 2-29), including how to assess RNase activity (*e.g.*, Example 7, page 43). The application also teaches how to produce and purify the ribonuclease (*see, e.g.*, the section starting at page 19, line 2 through page 29, line 26) and how to produce conjugate molecules, either chemically (*see, e.g.*, page 29, line 29 through page 31, line 31) or recombinantly (*see, e.g.*, page 32, line 2 through page 33, line 21). Thus, the disclosure in the specification, along with methodology well known to those of skill in the art, provide ample direction for screening ribonucleases having the claimed structural and functional characteristics.

In the present application, one of skill needs to identify ribonucleases that have a high level of identity with respected to a conserved reference sequence, specific residues at particular positions, and ribonuclease activity. Although many such ribonucleases are possible, one of skill can readily determine, one by one, any particular sequence that has these properties without undue experimentation.

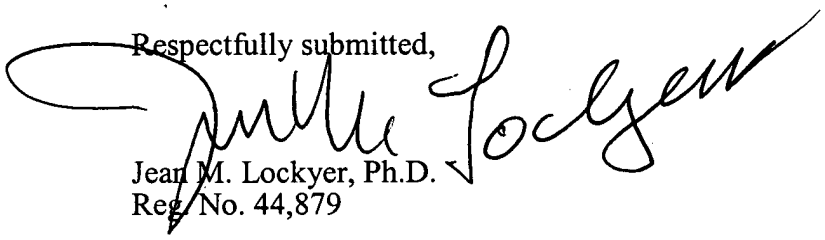
In light of the above arguments, Applicants respectfully submit that the claims are fully enabled, and request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Jean M. Lockyer, Ph.D.
Reg. No. 44,879

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
JML:jml
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